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M. M. SHEMYAKIN, M. N. KOLOSOV,

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Abstract

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Corresponding Member of the Academy of Sciences of the USSR M. M. SHEMYAKIN, M. N. KOLOSOV,
M. G. KARAPETYAN and E. S. CHAMAN

INITIAL STAGES OF THE SYNTHESIS OF TETRACYCLINES

Antibiotics of the tetracycline group—tetracycline (Ia) ([1,2]), terramycin (Ib) ([3]), aureomycin (Iv) ([2,4,5]), and bromotetracycline (Ig) ([6])—are of considerable interest and attract the attention of investigators because of their high antimicrobial activity and low toxicity.

However, despite the large number of works devoted to tetracycline antibiotics, not only has the synthesis of their specific ring system not yet been accomplished, but methods have not been developed for obtaining simpler substances having the groupings characteristic of tetracyclines. In considering possible routes for the synthesis of tetracyclines, such directions appear promising according to which the necessary substituents and functional groups are introduced into the molecule gradually, as the hydronaphthacene skeleton is constructed. In addition, it is desirable to carry out the construction of ring D on an already sufficiently prepared tricyclic ABC system, having the same spatial structure as the corresponding part of the tetracycline molecules.

In this connection we undertook the synthesis of tricyclic compounds of type (IV), possessing a structure of rings A and B similar to that of tetracyclines and having in ring C such groupings with the aid of which it would then be possible to construct ring D. The synthetic route chosen by us for compounds of this kind consists in the condensation of 1,4-naphthoquinones with butadiene or its derivatives, followed by conversion of the diketones (II) formed into compounds of type (IV) as a result of selective interaction of one of their carbonyl groups with CH_3MgJ. The first stage of the synthesis (diene condensation) proceeds in high yields on heating naphthoquinones with an excess of diene at 100°. Thus, on heating naphthoquinone with 2-methoxybutadiene for 4 hours in alcohol, compound (IIb) is formed in 88% yield (m.p. 143–144° from benzene. Found, %: C 74.08; H 5.93. $C_{15}H_{14}O_3$. Calculated, %: C 74.36; H 5.82); on heating 5-methoxynaphthoquinone with an alcoholic solution of butadiene for 1.5 hr, the adduct (IIv) is obtained in 91% yield (m.p. 92–93° from alcohol, λ_{max} (in alcohol) 229, 336 mμ ($\lg\varepsilon$ 4.41; 3.73). Found, %: C 74.49; H 5.89. $C_{15}H_{14}O_3$. Calculated, %: C 74.36; H 5.82), and from 5-acetoxynaphthoquinone and butadiene under analogous conditions, in 91% yield, diketone (IIg) is formed, existing

Reaction scheme with compounds II-IX and substituent definitions.

Figure 1: Reaction scheme with compounds II-IX and substituent definitions.

in two crystalline modifications (α and β)*. (α-form m.p. 113.5-114.5° from alcohol. Found, %: C 71.50; H 5.11. $C_{16}H_{14}O_4$. Calculated, %: C 71.10; H 5.22. β-form m.p. 135.5-136.5° from alcohol, λ_{max} (in alcohol) 223, 245, 307 mμ (lg ε 4.44; 3.91; 3.37). Found, %: C 71.29; H 5.20). The condensation of 5-methoxynaphthoquinone with 2-methoxybutadiene must be carried out in absolute benzene in an atmosphere of CO_2 (100°, 12 hr). The resulting mixture of isomeric adducts (yield 94%) is separated by fractional crystallization from benzene. One of the isomers, (IId), is obtained with—

* The α-form is metastable; in the melt or in solution it is readily converted into the stable β-form.

yield 55% (m.p. 144-145° (from benzene), λ_{max} (in alcohol) 227, 338 mμ (lg ε 4.32; 3.70). Found, %: C 70.72; H 6.13. $C_{16}H_{16}O_4$. Calculated, %: C 70.57; H 5.92), and the second isomer (IIe)—in 15% yield (m.p. 141-143° (from benzene), λ_{max} (in alcohol) 227, 338 mμ (lg ε 4.33; 3.72). Found, %: C 70.59; H 5.87).

The structures of the adducts (IId) and (IIe) were established by their oxidation with O_2 in alkaline alcoholic solution to dimethoxyanthraquinones (IIIa) (m.p. 192.2-192.6°) and (IIIb) (m.p. 189.5-189.9°), which were then hydrolyzed with 78% H_2SO_4 (160°, 30 min.) to dioxyanthraquinones (IIIv) (m.p. 293-294°) and (IIIg) (m.p. 281.5-282.5°), characterized as the diacetyl derivatives (IIId) (m.p. 197-198°) and (IIIe) (m.p. 204-205°) (cf. [7])*.

The execution of the second stage of the synthesis, i.e., the selective conversion of the keto group in position 10 into the tertiary methylcarbinol group, is associated with a number of difficulties because of the presence in the molecule of two reactive carbonyl groups and the tendency of adducts of type (II) to isomerize under the influence of enolizing agents into derivatives of dihydroanthrahydroquinone.

In this connection the reaction should be carried out by adding an ethereal solution of methylmagnesium iodide (excess not more than 25%) to a cooled benzene solution of the adduct (II). Under these optimum conditions the diketone (IIa) (for its preparation see [9]) is converted into the ketol (IVa) in 70% yield (m.p. 135-137° (from alcohol), λ_{max} (in alcohol) 248, 291 mμ (lg ε 3.95; 3.28). Found: C 79.24%; H 6.76%; active H 1.07. $C_{15}H_{16}O_2$. Calculated: C 78.90%; H 7.07%; active H 1.00), the adduct (IIv) forms the ketol (IVb) in 12% yield (m.p. 194-196° (from 50% alcohol), λ_{max} (in alcohol) 256, 317 mμ (lg ε 3.86; 3.68). Found: C 74.35%; H 7.11%; active H 1.05. $C_{16}H_{18}O_3$. Calculated: C 74.39%; H 7.02%; active H 1.00), and from compound (IId) a mixture of two isomeric keto alcohols (IVv) and (V) is obtained; first (IVv) crystallizes out (yield 12%, m.p. 191-193° (from benzene). Found: C 71.09%; H 6.78%; active H 0.95. $C_{17}H_{20}O_4$. Calculated: C 70.82%; H 6.99%; active H 1.00), and then its isomer (V) (yield

49%, m.p. 137.5–138.5° (from alcohol). Found: C 71.14%; H 7.05%; active H 1.01)**.

To determine the position of the methylcarbinol group in the ketol (IVb),

* V. Ya. Rodionov took part in this part of the investigations.
** In all these cases, along with the ketols (IV) and (V), small amounts of the corresponding dihydroanthrahydroquinones are obtained, formed as a result of isomerization and subsequent oxidation of the starting adducts (II).

(IVb) and (V) were converted (reaction conditions are given below) into 1,9- and 1,10-oxymethoxyhydroanthracenes (VIb), (VIIb), and (VIII). In a study of the infrared spectra of compound (VIIb) and of the dihydro derivative (VIIg) obtained from (VIb), a shift and broadening of the OH-group band were found [10], characteristic of compounds with an intramolecular hydrogen bond $-O(CH_3)\cdots HO-$(such as 1,8-oxymethoxynaphthalene, etc.); consequently these substances must be assigned the structure of derivatives of 1,9-oxymethoxyhydroanthracene. The frequency of the OH-group band in compound (VIII), however, corresponded completely to the OH frequency in 1,5-oxymethoxynaphthalene. It is also necessary to note that the almost complete identity of the ultraviolet spectra of compound (VIb) and its dihydro derivative (VIIg) (spectra are given below) indicates that the double bond in (VIb) is not conjugated with the aromatic system and, therefore, all transformations of adducts of type (II) are not accompanied by migration of the double bond from the 6,7-position.

Returning to the reaction of adducts (II) with methylmagnesium iodide, it should be noted that with a considerable excess of CH_3MgI and the reverse order of mixing of the reagents, i.e., when the adduct is added to the organomagnesium compound, the principal reaction products become glycols of type (VI). For example, from adduct (IIa) there is obtained glycol (VIa), which is then dehydrated to dimethyldihydroanthracene (IXa) (m.p. 166–167° (from benzene), λ_{max} (in alcohol) 238, 260, 285, 297 mμ (lg ε 4.78; 3.53; 3.76; 3.80). Found, %: C 92.52; H 7.63. $C_{16}H_{16}$. Calculated, %: C 92.25; H 7.75), from adduct (IIb) glycol (VIb) is formed in 40% yield (m.p. 171–172° (from methanol). Found, %: C 74.50; H 8.12. $C_{17}H_{22}O_3$. Calculated, %: C 74.42; H 8.08), and diketone (IIv) is converted in 49% yield into glycol (VIv) (m.p. 139–140° (from 50% alcohol), λ_{max} (in alcohol) 272, 279 mμ (lg ε 3.22; 3.22). Found: C 74.30%; H 8.12%; $H_{act.}$ 1.89. $C_{17}H_{22}O_3$. Calculated: C 74.42%; H 8.08%; $H_{act.}$ 2.00).

In contrast to the diketones (II), the ketols (IV) and (V), and also the glycols (VI), are quite stable toward alkalis. This undoubtedly shows that they have the more stable, i.e., trans, fusion of rings B and C (cf. the behavior of cis- and trans-α-decalones [11]). Consequently, in the formation of these ketols from adducts (II), epimerization of one of the asymmetric centers (C_{8a} or C_{10a}) takes place, since the initial adducts, according to Alder' s rule, must have the cis configuration. As for the third asymmetric center (C_{10}), its configuration can be established on the basis of the principle of "steric control of asymmetric induction" [12], according to which the methyl group at C_{10} must be in the cis

position to the hydrogen atom at C_{10a}. Thus, ketols of type (IV) evidently have the spatial structure (X), completely corresponding to the configuration of the natural tetracycline antibiotics (I) [3,4]. This is further confirmed by the fact that ketols of type (IV) undergo acid dehydration under the same conditions and with the same ease (see below) as tetracyclines (I); since the ease of these transformations is determined by the spatial mutual arrangement of the groups being split off, the identical behavior of ketols (IV) and tetracyclines (I) undoubtedly attests to the identity of the configurations of the corresponding portions of their molecules.

Being stable toward alkalis, the ketols (IV) and (V), as well as the glycols (VI), are very sensitive to the action of acidic agents. On heating these compounds with conc. aqueous-alcoholic HCl (60°, 20-30 min), their dehydration occurs, accompanied by aromatization of ring B, as a result of which derivatives of di- and tetrahydroanthracene are formed. Thus, ketol (IVa) is dehydrated to dihydroanthrol (VIIa) (yield 83%, m.p. 117-119° (from petroleum ether). Found: C 85.43%; H 6.85%; $H_{act.}$ 1.09. $C_{15}H_{14}O$. Calculated: C 85.68%; H 6.66%; $H_{act.}$ 1.00. Acetate,

m.p. 153-156° (from alcohol). Found, %: C 81.16; H 6.37. $C_{17}H_{16}O_2$. Calculated, %: C 80.93; H 6.39. Methyl ether, m.p. 97-99° (from alcohol), λ_{max} (in alcohol) 236, 288, 297 mμ ($\lg \varepsilon$ 4.65; 3.75; 3.79). Found, %: C 85.64; H 7.16. $C_{16}H_{16}O$. Calculated, %: C 85.66; H 7.26). Ketol (IVb) behaves analogously, being converted into dihydroanthrol (VIIb) (yield 96%, m.p. 115-116° (from heptane), λ_{max} (in alcohol) 241, 311, 324, 339 mμ ($\lg \varepsilon$ 4.60; 3.88; 3.91; 3.93). Found: C 80.20%; H 6.68%, H_{act} 0.96. $C_{16}H_{16}O_2$. Calculated: C 79.97%; H 6.71%; H_{act} 1.00. Dihydro derivative (VIIg), m.p. 107.5-108° (from alcohol), λ_{max} (in alcohol) 237, 312, 324, 339 mμ ($\lg \varepsilon$ 4.55; 3.86; 3.89; 3.90). Found: C 79.33%; H 7.55%; H_{act} 0.97. $C_{16}H_{18}O_2$. Calculated: C 79.30%; H 7.49%; H_{act} 1.00). Like the ketols (IV), glycol (VIb) is also readily dehydrated, forming dihydroanthracene (IXb) (yield 90%, m.p. 115-115.5° (from benzene), λ_{max} (in alcohol) 241, 296, 306, 319, 333 mμ ($\lg \varepsilon$ 4.59; 3.85; 3.92; 3.78; 3.49). Found, %: C 85.21; H 7.66. $C_{17}H_{18}O$. Calculated, %: C 85.68; H 7.61).

Ketols and glycols that are enol ethers (compounds IVb, V, and VIb), when heated with HCl under the above-stated conditions, are simultaneously dehydrated and hydrolyzed, forming the corresponding ketones of the tetrahydroanthracene series. Thus, ketol (IVb) is converted into keto-tetrahydroanthrol (VIIb) (yield 75%, m.p. 136-137° (from alcohol). Found, %: C 74.87; H 6.32. $C_{16}H_{16}O_3$. Calculated, %: C 74.99; H 6.28), ketol (V) forms the ketotetrahydroanthrol (VIII) isomeric with compound (VIIb) (yield 90%, m.p. 170-173°) (from alcohol). Found: C 75.30%; H 6.19%; H_{act} 1.02), and from glycol (VIb) ketotetrahydroanthracene (IXb) is obtained (yield 94%, m.p. 120-121° (from benzene)).

However, under milder conditions (shaking an ethereal solution of the substance with 1-2% HCl at 20°), it is possible selectively to hydrolyze the methoxyl group of ring C without affecting the tertiary hydroxyls of ring B; in this case, for

example, from glycol (VIb), along with a small amount (10–12%) of tetrahydroanthracene ketone (IXb), 2-keto-9,10-dioxy-9,10-dimethyl-1,2,3,4,4a,9,9a,10-octahydroanthracene is formed (yield 53%, m.p. 135–136° (from benzene). Found: C 73.86%; H 8.01%; H_{act} 2.06. $C_{16}H_{20}O_3$. Calculated: C 73.82%; H 7.73%; H_{act} 2.00).

Thus, the synthetic route we have developed makes it possible, starting from readily available 1,4-naphthoquinones, to obtain in two stages tricyclic ketols of type (IV), which have the same spatial structure as the natural tetracycline antibiotics. The presence in these ketols, in ring C, of a reactive double bond or carbonyl group creates the potential possibility of further introduction of substituents and then construction of the fourth ring of the tetracyclines.

Institute of Biological and Medicinal Chemistry
Academy of Medical Sciences of the USSR

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Note: Figure translations are in progress. See original paper for figures.